






ORIGINAL STUDIES

Amplatzer Piccolo Occluder clinical trial for percutaneous closure of the patent ductus arteriosus in patients ≥ 700 grams

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Abstract

Objectives: Characterize the safety and effectiveness of the Amplatzer Piccolo Occluder for patent ductus arteriosus (PDA) closure.

Background: The presence of a hemodynamically significant PDA has been associated with an increased risk of morbidity and mortality in children born premature.

Methods: This was a single arm, prospective, multicenter, non-randomized study to evaluate the Amplatzer Piccolo Occluder to treat PDA in patients ≥ 700 g. From June 2017 to February 2019, 200 patients were enrolled at nine centers, with 100 patients weighing ≤ 2 kg. Primary effectiveness endpoint was the rate of PDA closure at 6-month follow-up. Primary safety endpoint was the rate of major complications through 6 months. Secondary endpoint was rate of significant pulmonary or aortic obstruction through 6 months' follow-up.

Results: The implant success rate was 95.5% (191/200) overall and 99% in patients ≤ 2 kg (99/100). The primary effectiveness endpoint was achieved in 99.4% of implanted patients. Four patients experienced a primary safety endpoint event (2 transfusions, 1 hemolysis, and 1 aortic obstruction). There were no branch pulmonary artery obstructions. Five patients, all ≤ 2 kg, were noted to have worsening of tricuspid regurgitation (TR) after the procedure. None of the TR incidences manifested clinically. The Amplatzer Piccolo Occluder received FDA approval in January 2019 and became the first device approved for PDA closure in patients ≥ 700 g.

Conclusions: This study supports the safety and effectiveness of the Amplatzer Piccolo Occluder, particularly in patients between 700 g and 2 kg where there is currently a significant unmet need in the United States. ClinicalTrials.gov identifier: NCT03055858.

KEYWORDS

ADO II AS, Amplatzer Piccolo Occluder, FDA, patent ductus arteriosus, prematurity, transcatheter closure

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1 | INTRODUCTION

A patent ductus arteriosus (PDA) is a persistence of the fetal connection (ductus arteriosus) between the pulmonary artery and aorta after birth, typically resulting in a continuous left-to-right shunt. Presence of a PDA beyond the first week of life occurs in as many as 50% of premature babies and in more than 80% of severely premature extremely low birth weight (ELBW) infants (<1,000 g at birth).¹ Persistence of a hemodynamically significant PDA (hsPDA) in these children has been associated with an increased risk of developing necrotizing enterocolitis, chronic respiratory disease, pulmonary hemorrhage, intraventricular hemorrhage, and death.^{2,3}

Current treatment options for hsPDA closure in a premature infant include medical management or surgical ligation. Medical management aimed at closing the hsPDA typically consists of intravenous administration of cyclooxygenase inhibitors or acetaminophen, both of which are utilized off-label. Unfortunately, this treatment is effective in only approximately 50% of ELBW infants⁴ and is associated with significant side effects, including permanent or transient alterations in renal function, necrotizing enterocolitis, gastrointestinal perforation, and impairment of cerebral blood flow.⁴⁻⁶ Surgical ligation, while effective, has been associated with significant procedural and post-procedural complications and poor long-term outcomes, including worsening lung disease and poor neurodevelopmental outcomes.^{4,6} More recently there has been a trend toward permissive, conservative observation, reserving surgery for only the most severe cases.⁷⁻⁹ Recent data suggest that this approach may be associated with an increased risk of chronic lung disease and death, especially in infants born ≤ 26 weeks' gestation.¹⁰⁻¹² Therefore, the data on the association of PDA and outcomes is not conclusive one way or the other.

Transcatheter device closure of PDA is the standard of care in larger infants, children and adults.¹³ Historically, transcatheter closure of PDA has not been performed routinely in very small infants (weight ≤ 2 kg). Recently, a growing body of clinical evidence has emerged suggesting that transcatheter closure of PDA can be performed safely and effectively in premature infants¹⁴⁻¹⁹ as small as 700 g or smaller. The Amplatzer Piccolo Occluder (Abbott Structural Heart, Plymouth, MN), previously called the Amplatzer Duct Occluder II Additional Sizes (ADO II AS) obtained CE-Mark in Europe in 2011 for PDA closure in patients ≥ 6 kg. The PDA morphology in extremely premature infants resembles its fetal counterpart (so-called F-type PDA morphology). It is typically long and tubular with a hockey stick configuration²⁰ such that the Amplatzer Piccolo Occluder has favorable features (size, shape, delivery system) for closure of PDAs in premature neonates. A clinical study evaluating the safety and effectiveness of the Amplatzer Piccolo Occluder was conducted that led to the approval of this device by the U.S. Food and Drug Administration (FDA) for patients ≥ 700 g.

2 | METHODS

This was a single arm, prospective, multicenter, non-randomized clinical investigation designed to characterize the safety and effectiveness

of the Amplatzer Piccolo Occluder in patients ≥ 700 g. Patient follow-up occurred prior to hospital discharge and at 30 days and 6 months post-procedure. Additional follow-up visits will occur at 12, 24, and 36 months. The initial pivotal, investigational device exemption (IDE) protocol allowed for enrollment of 50 patients from up to 10 centers with a requirement for having at least 15 patients with a weight ≤ 2 kg at the time of procedure. Another 150 patients were later enrolled on a continued access protocol (CAP) under the same protocol. The combined results of the IDE and CAP are presented in detail in this study.

The primary effectiveness endpoint was the rate of effective PDA closure among patients with a successful Amplatzer Piccolo Occluder implant, as assessed by the presence of either no or trivial residual shunt (grade 0 or 1, with 2 being mild, 3 being moderate, and 4 being severe) at the 6-month follow-up by transthoracic echocardiography (TTE). The primary safety endpoint was the rate of major complications through 6 months after an attempted Amplatzer Piccolo Occluder implant. Major complications were defined as device- or procedure-related adverse events resulting in either death, a life-threatening adverse event, persistent or significant disability/incapacity, and/or a major open surgical intervention. The secondary endpoint was defined as the rate of significant obstruction of the left pulmonary artery (LPA) or the proximal descending thoracic aorta through the 6-month follow-up visit. Significant obstruction of the LPA was defined as a peak instantaneous Doppler gradient in the LPA ≥ 35 mmHg by echocardiogram. Significant obstruction of the aorta was defined as a mean Doppler gradient ≥ 20 mmHg in the aortic isthmus by echocardiogram.

Potential patients were screened using predetermined inclusion and exclusion criteria. Patients meeting all inclusion criteria and not meeting any exclusion criteria were enrolled in the study. Key inclusion criteria were the presence of a PDA ≤ 4 mm in diameter and ≥ 3 mm in length based on an intra-procedural echocardiogram or angiogram. Key exclusion criteria were: weight < 700 g and age < 3 days at time of the procedure, presence of a pre-existing coarctation of the aorta or LPA stenosis, pulmonary hypertension where cardiac output depended on a right to left shunt through the PDA, presence of an intracardiac thrombus, or active infection. An independent Echocardiography Core Laboratory (Core Lab) reviewed baseline and 6-month TTEs for IDE and CAP patients. Independent adjudication of pre-defined clinical events, including major and minor complications and deaths, was performed by a clinical events committee (CEC).

2.1 | Description of the procedure

The Amplatzer Piccolo Occluder is a self-expandable, Nitinol mesh device with a central cylindrical waist and low-profile retention discs that are marginally larger than the waist, resulting in a nearly isodiametric device (Figure 1). The device comes pre-loaded on a delivery wire, which has a soft floppy distal end with a microscrew attachment at the tip. It can be delivered through a 4 F Amplatzer TorqVue LP catheter (Abbott Structural Heart, Plymouth, MN). The Amplatzer Piccolo Occluder is available in nine sizes (Figure 1) comprised of three waist diameters (3, 4, and 5 mm) and three lengths (2, 4, and 6 mm).

The Amplatzer Piccolo Occluder, because of the symmetrical configuration, can be delivered either antegrade via the femoral vein or retrograde via the femoral artery. In children ≤ 2 kg, special procedural modifications were utilized to avoid the need for vascular access into the femoral artery in order to maximize safety and avoid complications (Table 1, Figures 2 and 3).

2.2 | Statistical methods

This is a descriptive study. Categorical data are reported as a count and percentage. Continuous data are reported as mean \pm SD unless otherwise specified. The range is also provided to present the minimum and maximum values.

3 | RESULTS

Between the IDE and the CAP studies, 200 patients were enrolled from nine centers including 100 patients ≤ 2 kg at the time of the

procedure. Demographics and baseline characteristics are presented in Table 2. The youngest patient was 10 days old, with the smallest patient weighing 700 g. There were 33 patients who were ≤ 1 kg at the time of the procedure. A histogram depicting gestational age and patient weight (Figure 4a,b) shows a bimodal distribution with two distinct patient populations: ≤ 2 and > 2 kg. The gestational age at birth ranged from 22 to 34 weeks (Figure 4c). Among patients > 2 kg there were 50 patients with weights between 2 kg and 6 kg. All 100 patients ≤ 2 kg were in the neonatal intensive care unit (NICU) at the time of the procedure. However, only 32 patients that were > 2 kg were from the NICU. A long and tubular PDA (type C or F) was observed in 86% of patients ≤ 2 kg (Figure 5a,b), while a conical PDA (type A) was observed in 43% of patients > 2 kg (Figure 5a,c). Despite the smaller size of patients ≤ 2 kg, the mean PDA length was 10.6 ± 2.2 mm compared to a mean PDA length of 10.1 ± 3.4 mm in patients > 2 kg.

Procedure characteristics are shown in Table 3. An antegrade implant approach was used in all patients ≤ 2 kg. An anterograde implant was performed in 73.9% of patients > 2 kg. The femoral artery was accessed in 48% of patients > 2 kg. Heparin usage varied between groups, with 16% of patients ≤ 2 kg receiving a heparin bolus during

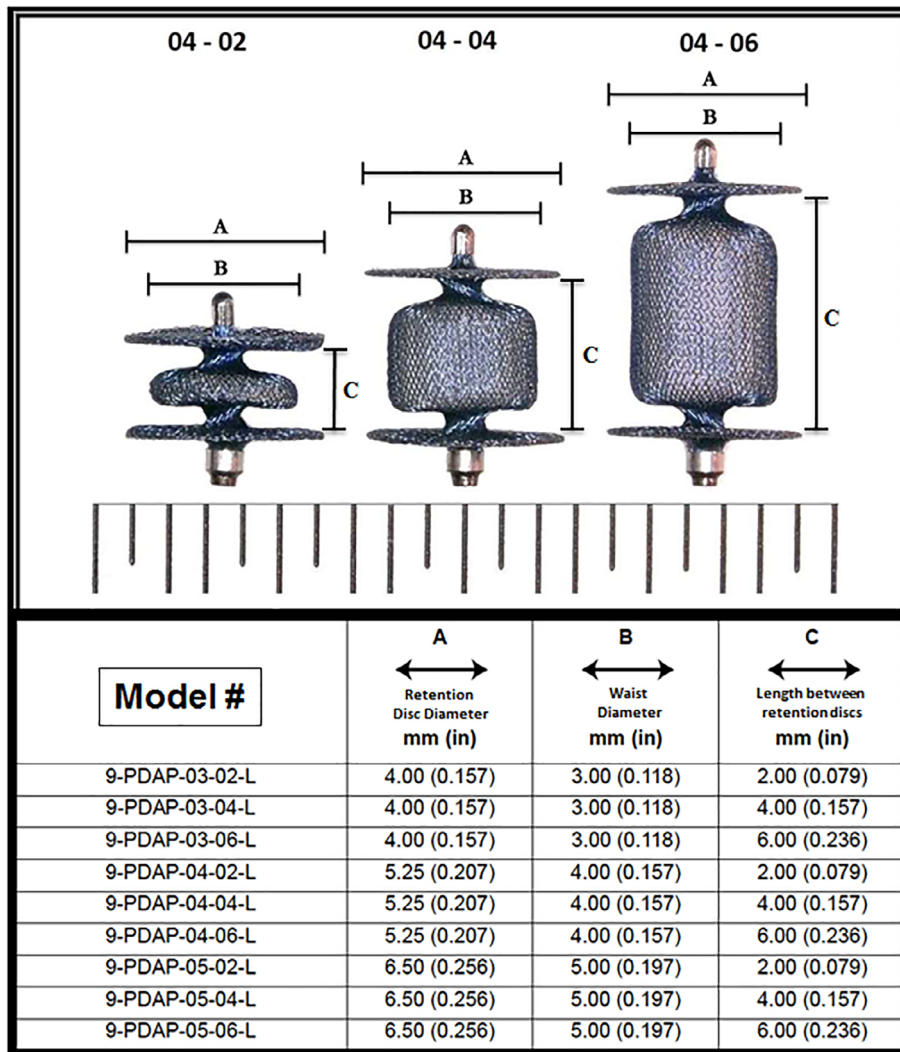
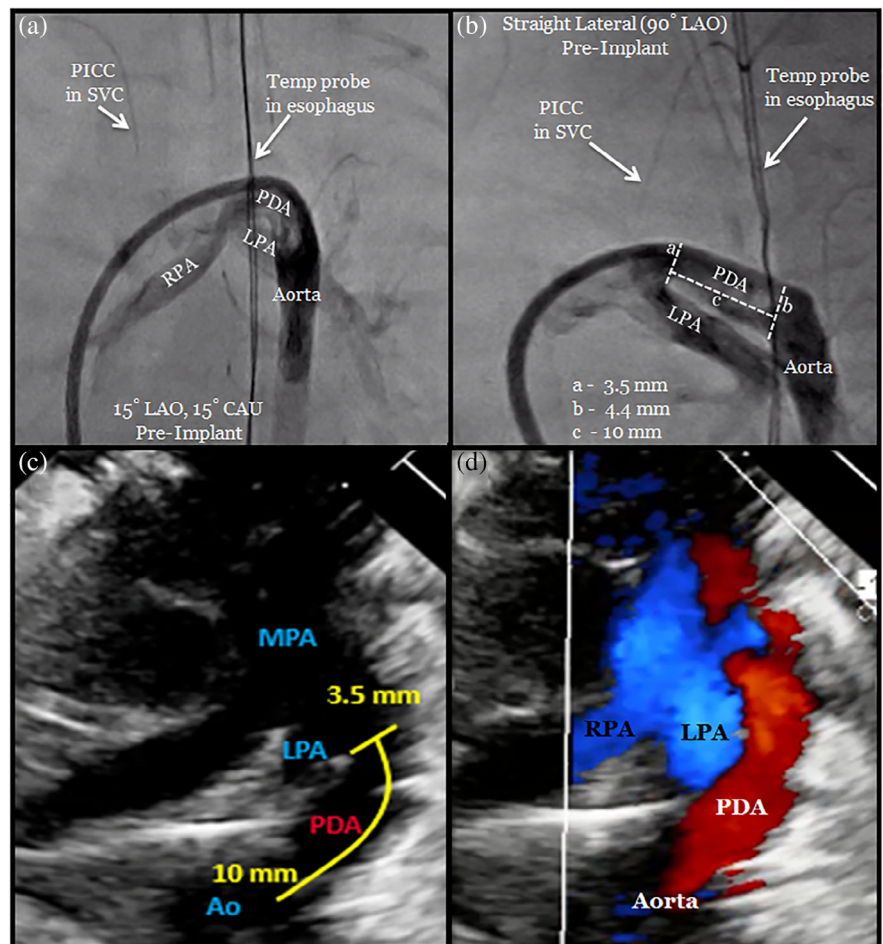


FIGURE 1 High-resolution photographs of the 4 mm Amplatzer Piccolo Occluder of three different lengths [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Procedural modifications in children ≤ 2 kg

1. Femoral arterial access must be avoided.^{21,22} All cases were performed in this population from the femoral vein.
2. In most cases angiographic measurements as well as measurements made by TTE of the PDA were used to select device size (Figure 2).
3. Following device deployment, in the absence of an arterial catheter (i.e., no ability to perform aortography), TTE was heavily relied upon²³ to assess aortic flow, residual PDA shunting and LPA flow (Figure 3).
4. Device selection and sizing:
In larger children (>2 kg) the device size is selected so that the central waist spans the entire length of the duct with the retention discs placed just outside the duct (extraductal disc placement) to achieve improved positional stability and minimize the potential for device embolization. However, when treating small infants, especially those ≤ 2 kg, the entire device with both retention discs is implanted completely within the duct (intraductal placement) to minimize the potential for protrusion into the aorta or the LPA and to avoid inadvertent stenosis of these vessels by the device discs.^{15,17,24} Therefore, device size selection in children ≤ 2 kg was based on achieving adequate compression of the disc and favoring a shorter device length (2 mm).
5. Following deployment, but prior to device release, in addition to echocardiographic assessment as noted above, angiography was often performed via a Touhy-Borst attached to the end of the TorqVue LP catheter to check for stenosis of the proximal LPA caused by the device (Figure 4) and for aortic arch stenosis on levophase. A left anterior oblique view with slight caudal angulation (Figure 4) and straight lateral projections were useful to assess the proximal LPA. Palpation of the femoral artery pulse, and/or use of non-invasive blood pressure monitoring in a lower extremity were other useful techniques used to monitor for the presence of aortic obstruction following device deployment in conjunction with TTE assessment. LPA angiogram is unnecessary following device release. TTE alone will suffice.
6. Additional useful tips for implantation in children ≤ 2 kg:
 - a A central venous catheter tip in the superior vena cava (SVC), when present, consistently provided a useful landmark for the pulmonary end and an esophageal feeding tube or temperature probe provided a consistently useful landmark of the aortic end of the PDA on lateral fluoroscopy (Figure 4).
 - b Increased attention and accommodations were made for
 - i Transport to-and-from the neonatal intensive care unit (NICU)²⁵;
 - ii Procedural mechanical ventilator support;
 - iii Temperature control.

FIGURE 2 PDA Assessment prior to closure in an 800 g, 21-day-old, ex-24-week gestational age infant using echocardiographic and radiologic landmarks. (a) Angiogram obtained in the PDA in a left anterior oblique projection and caudal projection prior to device closure demonstrates the PA bifurcation clearly. The PDA is completely to the left of the esophageal temperature probe. (b) Angiogram obtained in the PDA in straight lateral projection, demonstrates a large fetal type (Type-F) PDA. The temperature probe in the esophagus marks the aortic end of the PDA and the tip of a peripherally inserted central catheter (PICC) in the superior vena cava (SVC) marks the pulmonary end of the PDA. The PDA is typically measured in this projection. (c) TTE of a large fetal type (Type-F) PDA in a parasternal short axis view. The measurements are best made in this projection. The length is typically made in a curvilinear fashion as the PDA is hockey stick shaped. (d) Color Doppler interrogation in the parasternal short axis view prior to device closure demonstrates continuous left to right shunt across the PDA [Color figure can be viewed at wileyonlinelibrary.com]



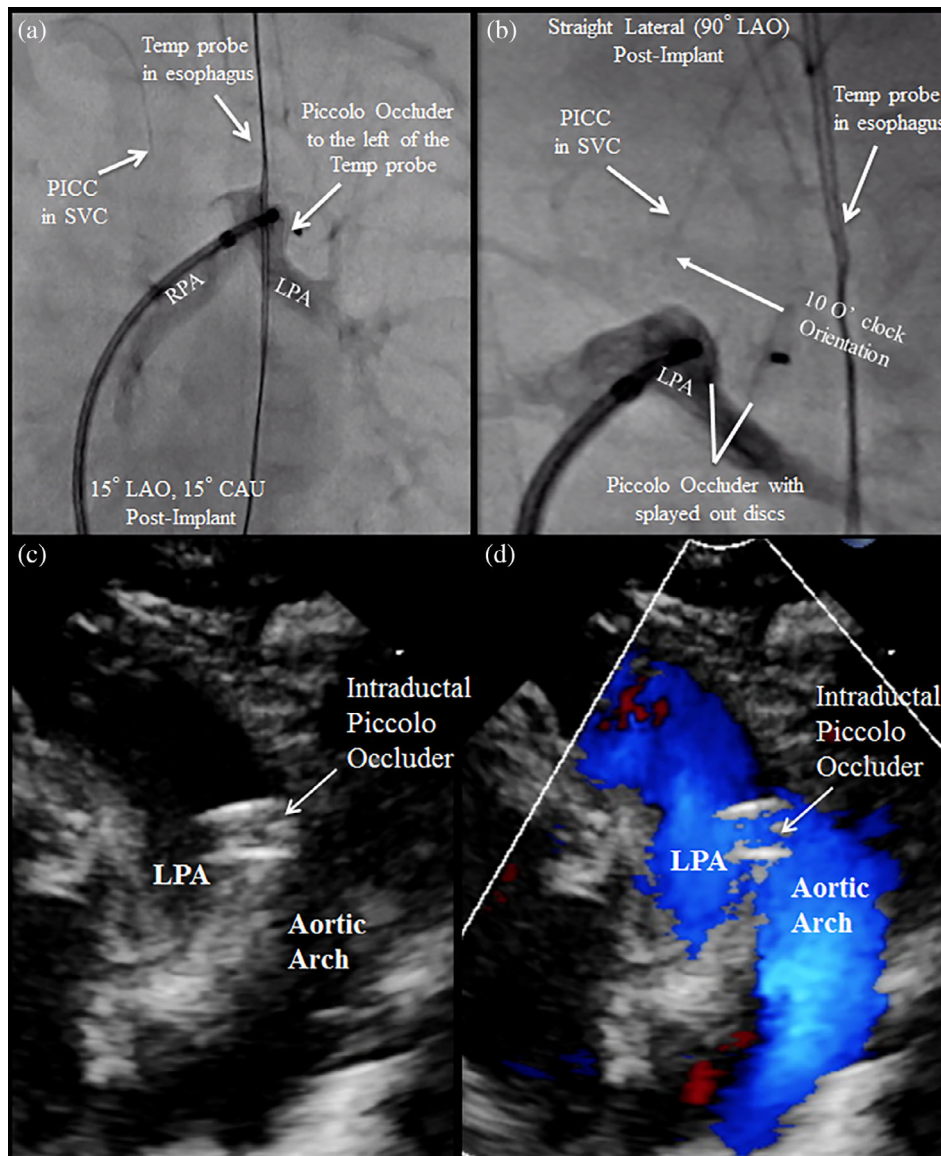


FIGURE 3 PDA occlusion using the 4-2 Amplatzer Piccolo Occluder in an 800 g, 21 days old, ex-24-week gestational age infant (same patient in FIGURE 2). (a) Angiogram obtained via the TorqVue LP catheter prior to releasing the device in left anterior oblique projection and caudal projection, demonstrates no LPA stenosis. The device is entirely to the left of the esophageal temperature probe. (b) Angiogram obtained via the TorqVue LP catheter prior to releasing of the device in straight lateral projection, demonstrates no LPA stenosis. The device is entirely intra-ductal and is positioned between the esophageal temperature probe and the PICC in the SVC. The device is splayed out along the long axis (superior edge) of the PDA and splayed together along the short axis (inferior edge) of the PDA—making a “Pac-Man” configuration. The orientation of the device along the long axis of the PDA (10 o’ clock position) is a good indication of proper device position. (c) 2D view from the suprasternal notch immediately after device implantation within the PDA demonstrates a completely intra-ductal location of the device with no stenosis of the LPA or the aorta. (d) Color Doppler interrogation from the suprasternal notch immediately after device implantation within the PDA confirms no residual shunt and no stenosis of the LPA or the aorta [Color figure can be viewed at wileyonlinelibrary.com]

the implant procedure compared to 61% of patients >2 kg. The shortest devices (03-02, 04-02, or 05-02) were implanted in 83.8% of patients ≤2 kg. A wider range of device sizes was used in patients >2 kg; however, the longest devices (6 mm) were only used in 11 patients all of whom were patients >2 kg.

Procedural outcomes are presented in Table 4. The Amplatzer Piccolo Occluder was successfully implanted in 92% of patients >2 kg, and 99% of patients ≤2 kg. In six of the eight patients >2 kg that had

an unsuccessful implant, the device was not released due to inability to achieve a stable position; of these six, three of whom had another PDA device implanted, two patients underwent successful surgical ligation and in one patient the procedure was postponed to a future date. Two other patients >2 kg had intra-procedural device embolizations. In both cases, the device was retrieved with a gooseneck snare and successfully removed from the body. Both patients were successfully implanted with a different commercially available device during

TABLE 2 Demographics and baseline characteristics

Characteristic	≤2 kg (N = 100)	>2 kg (N = 100)	Total (N = 200)
Demographics			
Age at procedure, months	1.25 ± 0.60 [0.30, 3.15]	26.58 ± 44.32 [0.49, 216.80]	3.92 ± 33.74 [0.30, 216.80]
Sex, male	60 (60.0%)	42 (42.0%)	102 (51.0%)
Procedure weight (kg)	1.25 ± 0.35 [0.70, 2.00]	11.25 ± 13.52 [2.02, 68.50]	6.25 ± 10.77 [0.70, 68.50]
Referred from NICU	100 (100.0%)	32 (32.0%)	132 (66.0%)
PDA type			
Type A—conical	6 (6%)	43 (43%)	49 (24.5%)
Type B—window	1 (1%)	2 (2%)	3 (1.5%)
Type C—tubular	16 (16%)	12 (12%)	28 (14%)
Type D—saccular	0 (0%)	5 (5%)	5 (2.5%)
Type E—elongated	5 (5%)	13 (13%)	18 (9%)
Type F—fetal	70 (70%)	21 (21%)	91 (45.5%)
Other/unknown	2 (2%)	4 (4%)	6 (3%)
Angiographic measurement of PDA			
	n = 98	n = 97	n = 195
Minimal PDA diameter (mm)	2.8 ± 0.7 [1.4, 4.0]	2.4 ± 0.7 [1.0, 4.0]	2.6 ± 0.7 [1.0, 4.0]
Maximal PDA diameter (mm)	4.1 ± 0.6 [2.0, 6.0]	5.2 ± 1.8 [2.0, 12.8]	4.6 ± 1.5 [2.0, 12.8]
PDA length (mm)	10.6 ± 2.2 [5.3, 19.2]	10.1 ± 3.4 [4.1, 20.0]	10.4 ± 2.9 [4.1, 20.0]

Note: Data presented as mean ± SD, range [minimum, maximum] for continuous variables or number of patients (percentage) for binary variables.

the same procedure. The one patient ≤2 kg that had an unsuccessful implant was due to inability to achieve a stable position. This patient underwent successful surgical ligation.

Intra-procedural device embolization occurred in five patients (two ≤2 kg and three >2 kg). All were successfully retrieved during the procedure with a gooseneck snare, without the need for an open surgical procedure. Following retrieval, both patients ≤2 kg had successful closure using a larger Amplatzer Piccolo Occluder. Of the three patients >2 kg that had intra-procedural device embolization, one had a larger Amplatzer Piccolo Occluder implanted while two were occluded with another commercially available device, all during the same procedure. The latter two patients were considered to have unsuccessful implants as described earlier.

Post-procedural device migration occurred in two patients (one ≤2 kg and one >2 kg). One patient weighing 1.6 kg experienced device migration 1 day post-procedure. The device migrated partially out of the PDA toward the pulmonary artery with evidence of a new moderate residual shunt and new LPA stenosis. For these reasons the device was snared and retrieved using a transcatheter approach into a long 4-French sheath. The PDA spontaneously closed and did not reopen following the procedure. The other patient that weighed 4 kg at the time of the procedure was noted to have device partially protruding into the LPA from the PDA with a moderate residual shunt. Decision was made to observe this patient as there were no clinical manifestations with the hope that the shunt would eventually cease. The residual shunt persisted for 189 days; at which time the patient was taken to the cardiac catheterization laboratory to plug up the residual shunt. However, during this procedure, the device was actually successfully snared and retrieved, and the PDA was occluded using a commercially available device.

In patients with a successful Amplatzer Piccolo Occluder implantation and a 6-month follow-up TTE, the effective closure rate, defined as no or trivial residual PDA shunt assessed by the Core Lab, was 100% in patients (89/89) ≤2 kg and 98.8% (83/84) >2 kg. The Core Lab was unable to determine shunt grade in two patients due to incomplete imaging views, but the sites reported residual shunting was none or trivial for both of these patients. Eleven patients were lost to follow-up prior to the 6-month follow-up visit and seven subjects did not complete the 6-month follow-up visit.

Among patients with a successful implant there were no instances of clinically significant LPA obstruction through 6-months of follow-up. There were two instances of aortic obstruction with only one event meeting the primary safety endpoint. One patient (procedure weight 1,100 g) had a mild coarctation of aorta prior to the procedure, which was an exclusion criterion; however, the decision was made to proceed with PDA closure using Amplatzer Piccolo Occluder in light of the patient's overall clinical scenario with the belief that the coarctation would remain mild and the patient would benefit by eliminating the large PDA. A 05-02 device was successfully implanted, but echocardiography within 72 hr of implant demonstrated progression to severe coarctation in the juxtaductal position, unrelated to device positioning. An intravascular stent was successfully implanted in the aortic segment with the coarctation 3 days post-procedure from a carotid approach. Ultimately, this patient underwent successful surgical coarctation repair at 16 months of age. The CEC adjudicated this event as not related to the device or the implant procedure and did not meet the primary safety endpoint for the trial. Another patient (procedure weight 760 g) experienced device-related obstruction of the aorta 6 days

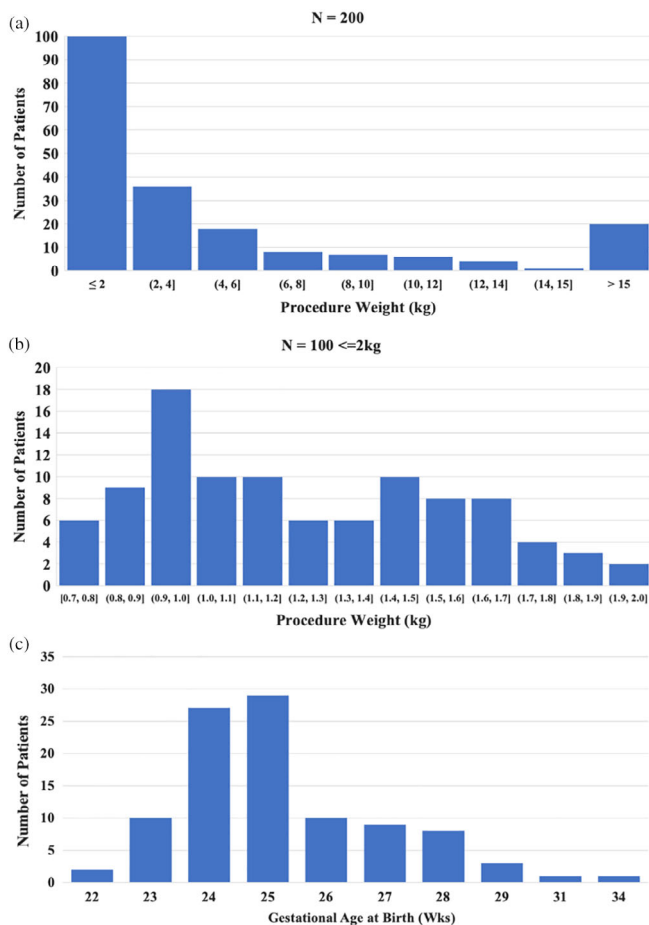


FIGURE 4 Histograms. (a) Histogram of patient weights of the 200 patients enrolled in the U.S. IDE and the CAP studies. (b) Histogram of weight distributions for patients ≤ 2 kg ($N = 100$). (c) Histogram of gestational age at birth for patients ≤ 2 kg ($N = 100$) [Color figure can be viewed at wileyonlinelibrary.com]

post-procedure which was also treated by stent implantation from a carotid approach. This patient died 14 days post-procedure secondary to severe respiratory failure and severe pulmonary hypertension leading to cardiorespiratory arrest. Three additional patients, all ≤ 2 kg experienced other complications. Two patients experienced blood loss requiring transfusion of ≥ 20 ml/kg of packed red blood cells. One patient with a history of congenital thrombocytopenia experienced hemolysis secondary to residual shunting through the device and received multiple blood and platelet transfusions. A repeat echocardiogram 46 days post-procedure revealed no residual shunt and the hemolysis resolved without sequelae.

Additionally, five patients (weight range 0.9–1.6 kg) developed new onset moderate tricuspid regurgitation (TR) post procedure. Two of these events occurred in patients who required device retrieval due to device embolization/migration. Of the five patients, at 6-month follow-up, two continued to have moderate TR, and one, mild TR. One patient died prior to the 6-month follow-up due to an unrelated condition. One patient was withdrawn from the study following device retrieval 1 day post procedure.

The overall survival for the IDE and CAP patients at 6 months was 96% for those ≤ 2 kg and 98% for those > 2 kg at the time of the procedure.

4 | DISCUSSION

A widely recognized unmet need for a PDA closure device suitable for premature infants to treat hsPDA led pediatric interventional cardiologists to reapproach industry in 2015 and to work collaboratively with the FDA to define the best pathway for bringing the ADO II AS (Amplatzer Piccolo Occluder) to the United States. After several interactive discussions with the FDA, a consensus and design were reached for this IDE study. The relatively small sample size of 50 patients for the IDE was justified on the basis that ADO II AS was a line extension to the first and second generations of Amplatzer Duct Occluders and that the device has been used extensively outside the United States since 2011. Additionally, a body of published clinical experience with the device from outside the United States,^{26–35} provided reasonable assurance that the device had acceptable procedural safety and effectiveness in a real-world setting, including in infants < 2 kg.

Clinical outcomes derived from the IDE and CAP studies support the safety and effectiveness of the Amplatzer Piccolo Occluder device for PDA closure in pediatric patients. The Amplatzer Piccolo Occluder was successfully implanted in 95.5% of all study patients, including 99% of patients ≤ 2 kg. Effective ductal closure was documented in 99.4% of all implanted patients with a 6-month TTE evaluable by an independent Echocardiography Core Lab. Four patients experienced events adjudicated by the CEC as a major complication. The implant success rate and closure rate observed in this study are similar to those derived from a literature review (Table 5) involving patient-level data from 277 patients reported in ten peer reviewed manuscripts^{26–35} from medical centers in Italy, Ireland, United Kingdom, Turkey, Spain, France and Israel, receiving the ADO II AS (95.3% for patients ≤ 2 kg, 93.2% for patients 2–6 kg, and 100% for patients > 2 kg). FDA approval of the Amplatzer Piccolo Occluder was obtained on January 11, 2019. The patients from the IDE and CAP studies will continue to be followed for a total of 3 years post-implant to ensure longer term safety and effectiveness of the device.

The Amplatzer Piccolo Occluder is the first commercially available device for use in premature infants ≥ 700 g in the United States. Significant procedural complications can occur, especially with the smallest of patients^{15,17,29} despite the excellent outcomes in this study. While most pediatric interventional cardiologists are quite familiar with the technique of PDA closure, we believe that for infants ≤ 2 kg, several important procedural modifications (Table 1) are necessary to achieve the high procedural success and minimal complication rates observed in this study. Tricuspid regurgitation, albeit not clinically significant, was the most common complication. We speculate that the possible mechanisms for TR could be secondary to mismatch between the size of the guide wire and the catheter lumen, stiffness of the delivery system, and excessive catheter manipulations

FIGURE 5 PDA morphology. (a) Illustration of the six morphologic types of PDA used for classification in the US IDE and the CAP studies. (b) PDA morphology for patients ≤ 2 kg ($N = 100$) dominated by the fetal type (Type-F) morphology. (c) PDA morphology for patients >2 kg ($N = 100$) dominated by the conical type (Type-A) morphology [Color figure can be viewed at wileyonlinelibrary.com]

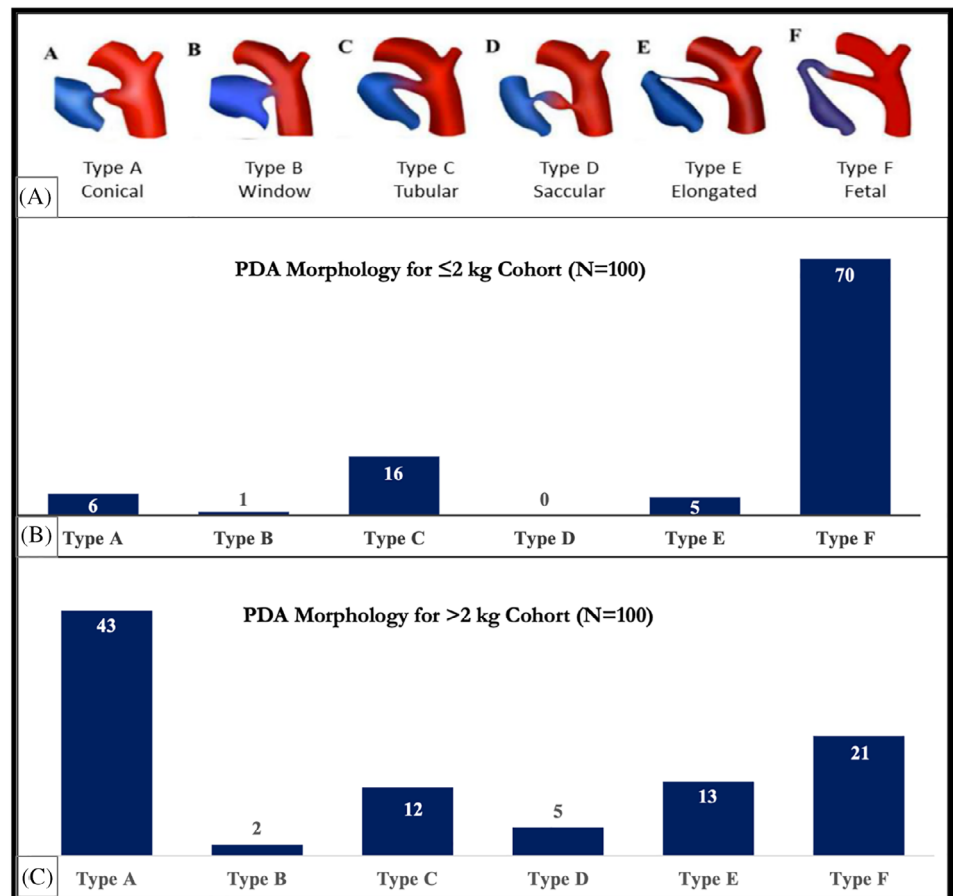


TABLE 3 Procedure characteristics

	≤ 2 kg ($N = 100$)	>2 kg ($N = 100$)	Total ($N = 200$)
Procedure time (min)	49.0 \pm 31.8 [14, 230]	57.1 \pm 29.3 [22, 202]	53.0 \pm 30.8 [14, 230]
Fluoroscopy time (min)	10.5 \pm 12.4 [3, 103]	10.1 \pm 7.0 [3, 43]	10.3 \pm 10.0 [3, 103]
Anterograde implant Approach ^a	99/99 (100.0%)	68/92 (73.9%)	167/191 (87.4%)
Femoral arterial access used	2 (2.0%)	48 (48.0%)	50 (25.0%)
IV contrast (ml/kg)	2.58 \pm 1.71 [0.00, 8.70]	2.37 \pm 1.59 [0.35, 8.55]	2.47 \pm 1.65 [0.00, 8.70]
Heparin usage	16 (16.0%)	61 (61.0%)	77 (38.5%)
Device sizes ^a	$n = 99$	$n = 92$	$n = 191$
03-02	8 (8.1%)	4 (4.3%)	12 (6.3%)
03-04	1 (1.0%)	4 (4.3%)	5 (2.6%)
04-02	59 (59.6%)	17 (18.5%)	76 (39.8%)
04-04	13 (13.1%)	17 (18.5%)	30 (15.7%)
04-06	0 (0.0%)	1 (1.1%)	1 (0.5%)
05-02	16 (16.2%)	12 (13.0%)	28 (14.7%)
05-04	2 (2.0%)	27 (29.3%)	29 (15.2%)
05-06	0 (0.0%)	10 (10.9%)	10 (5.2%)

Note: Data presented as mean \pm SD, range [minimum, maximum] for continuous variables or number of patients (percentage) for binary variables.

especially while retrieving an embolized device. Other factors we believe may be important in this unique population include minimizing intracardiac catheter manipulations, minimizing contrast dosing and avoiding unnecessary hemodynamic measurements to maintain short

procedure times. Anesthetic considerations include avoidance of inhalational agents especially for infants ≤ 2 kg, judicious use of benzodiazepines and opiates and, reducing dead space ventilation. All centers involved in the study experienced a significant learning curve in terms

TABLE 4 Outcomes

	≤2 kg (N = 100)	>2 kg (N = 100)	Total (N = 200)
Implant success (%)	99 (99.0%)	92 (92.0%)	191 (95.5%)
Intra-procedural device embolization rate (%)	2 (2.0%)	3 (3.0%)	5 (2.5%)
Post-procedure device migration rate (%) ^a	1/99 (1.01%)	1/92 (1.09%)	2/191 (1.05%)
Rate of effective closure at 6 months (%) ^b	89/89 (100.0%)	83/84 (98.8%)	172/173 (99.4%)
Rate of major complications through 180 days (%)	4/96 (4.2%)	0/98 (0%)	4/194 (2.1%)
Rate of clinically significant obstruction of the LPA or aorta through 6-months (%) ^a	2/99 (2.02%)	0/92 (0.0%)	2/191 (1.05%)
Rate of tricuspid valve regurgitation (%)	5 (5.0%)	0 (0.0%)	5 (2.5%)

Note: Data presented as number of patients (percentage) for binary variables.

^aDenominator is based on subjects with successful implant only.

^bOnly the sizes used are reported, the 03-06 size was not used.

TABLE 5 Patient-level data from 277 patients receiving ADO II AS in 10 European medical centers²⁶⁻³⁵

	≤2 kg (N = 169)	2–6 kg (N = 59)	>6 kg (N = 49)
Weight (kg)	1.28 ± 0.35 [0.68, 2.0]	3.4 ± 1.1 [2.1, 6.0]	14.6 ± 11.7 [6.2, 57]
PDA diameter (mm)	2.7 ± 0.8 [1.0, 4.2]	2.8 ± 0.8 [1.3, 4.0]	1.9 ± 0.5 [1.0, 3.2]
PDA length (mm)	6.8 ± 1.9 [2.6, 10.6] ^a	6.0 ± 2.5 [3.7, 13.0]	6.4 ± 2.5 [2.0, 11.2]
Successful implant	161 (95.3%)	55 (93.2%)	49 (100%)
Residual shunt at follow-up among successful implants	0 (0%)	0 (0%)	0 (0%)

Note: Data presented as mean ± SD, range [minimum, maximum] for continuous variables or number of patients (percentage) for binary variables.

^aIndividual data not available for PDA length (n = 26).

of caring for these very small patients in a cardiac catheterization laboratory environment, and utilization of a multidisciplinary team including the interventional cardiology team, cardiac anesthesia, neonatology and non-invasive imaging is critical to procedural success. In patients ≤2 kg undergoing this procedure, there is a particularly heavy reliance on TTE²³ during the procedure, which is something most cardiac catheterization programs do not routinely utilize intra-procedurally. A comprehensive training and proctoring program has been developed to ensure a responsible and safe dissemination of this technology to new users and proper implementation of the modified implant technique in infants ≤2 kg.

PDA morphology is fairly uniform and predictable in ELBW infants.²⁰ Typically, the duct is long and tubular, with a hockey stick-like appearance. This allows for implantation of the entire device within the PDA itself, limiting or completely avoiding inadvertent LPA or aortic obstruction by device discs.^{15,17,18,24} In general, a shorter device length (2 mm) is best suited in the smallest of patients. In the current study, all infants ≤2 kg had intraductal placement of the device with 83.8% (83/99) of infants receiving a device 2 mm in length.

There are certain limitations to this study. The trial was aimed at demonstrating feasibility and safety of the Amplatzer Piccolo Occluder for PDA closure in infants ≥700 g. This study was not designed to demonstrate benefits of the procedure in premature infants. Certain vital data including anesthetic exposure; outcome measures such as number of days of mechanical ventilation, oxygen

supplementation and hospitalization days were not collected as part of this study. The study also does not address other important questions such as optimal timing of the procedure in premature infants, compare outcomes with other traditional therapies such as surgical ligation and pharmacotherapy, nor does it suggest a treatment algorithm for this extremely vulnerable population. However, this study led to the approval of the device to be used in premature infants in the United States. Therefore, it serves as the first step toward future trials that could be aimed at demonstrating benefit.

The FDA approval of the Amplatzer Piccolo Occluder will facilitate treatment of numerous children who are born prematurely in the U.S. Currently, the benefit of PDA closure in premature infants is questioned yet is based solely on historical literature on surgical ligation and pharmacotherapy.⁷⁻⁹ At present, there is also no consensus on the ideal timing for PDA closure in premature infants.³⁶ Transcatheter PDA closure for ELBW and premature infants is a new therapy that could shift the treatment paradigm. Future studies are necessary to continue to answer important questions of which PDAs require closure and when to close the hsPDA in premature infants.

5 | CONCLUSIONS

The US IDE and CAP studies support the safety and effectiveness of the Amplatzer Piccolo Occluder, particularly in patients ≤2 kg, in whom there was a significant unmet need. The collaborative FDA

process which ultimately led to approval of this device may serve as a model for future device trials in the currently underserved pediatric space. Transcatheter PDA closure for premature infants is a less invasive alternative to surgical ligation. The benefit of this intervention over other therapies must be demonstrated before it can be fully adopted and become standard of care for premature infants.

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CONFLICT OF INTEREST

S. Sathanandam: proctor/consultant Abbott; D. Gutfinger: full-time employee Abbott; L. O'Brien: full-time Abbott employee; T. Forbes: proctor/consultant Abbott, Edwards, AcuNav/Biosence Webster, B. Braun Medical, Siemens, Medtronic; M. Gillespie: proctor/consultant Abbott; D. Berman: proctor/consultant Abbott, Edwards, Medtronic; A. Armstrong: proctor/consultant Abbott, Edwards, Medtronic, B. Braun; S. Shahanavaz: proctor Abbott, Medtronic, and Edwards; T. Jones: research grant, proctor/consultant Abbott, Edwards, Medtronic, W.L. Gore & Assoc.; B. Morray: Consultant Medtronic, proctor Abbott; T. Rockefeller: proctor Abbott; H. Justino: proctor/consultant Abbott, Edwards Lifesciences, Medtronic; Clinical trial executive committee Janssen Pharmaceutical; Co-founder PolyVascular; scientific advisory board Pediastent; D. Nykanen: proctor Abbott, consultant and independent data reviewer W.L. Gore & Assoc, expert witness Glaxo Smith Kline; E. Zahn: consultant/proctor Abbott, Edwards, Medtronic, National PI ADO II AS IDE Trial and Alterra/S3.

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